

REMARKS

Claims 1, 4, and 7-24 are pending. The Applicants respectfully request the Examiner to reconsider the rejections in view of amendments to the claims now presented and the following remarks.

Rejection under 35 USC §112, paragraph 1

The Applicants herein present amendments to claims 1, 18, and 20-21, which fundamentally incorporate the language “consisting of” thereby limiting the scope of the claims as recommended by the Examiner. Particularly, the pharmaceutical compositions now *positively* require tocoferol wherein the tocoferol consists of tocoferol covalently linked to a water-soluble polymer. Accordingly, the Applicants respectfully request the Examiner to withdraw the rejection.

Rejection under 35 USC §112, paragraph 2

The language “or derivatives thereof” is now deleted from claims 7-8 now presented. Further, the Applicants have amended claims 10 and 19 to particularly refer to TPGS or a derivative thereof formed by attaching a polymer on the tocoferol succinate portion or by attaching TPGS to the hydroxyl group of polyethylene glycol (PEG). Support for the amendment may be found in the specification, for example, at page 12, lines 11-13. The Examiner is also respectfully referred to page 14, line 10 *et seq*, of the specification for a detailed description of the entities. Accordingly, the Applicants respectfully request the Examiner to withdraw the rejection.

Rejection under 35 USC §103

The Examiner, from the record, appears to have previously construed the Applicants’ claims as encompassing compositions which comprise tocoferol, *per se*, as an independent chemical entity. The Applicants, however, as highlighted *supra*, now positively and unambiguously claim compositions that require tocoferol wherein said tocoferol is limited to tocoferol covalently linked to a water-soluble polymer. In sharp contrast, all compositions contemplated within the disclosure of Lambert, *et al*, ‘373, including Example 23, expressly

require tocoferol, *per se*, as an independent chemical entity (“[t]he compositions of this invention contain α -tocopherol as a carrier for therapeutic drugs”). See, e.g., ‘373 Col. 9, lines 14-15; Col. 21, line 49. Therefore, the Applicants respectfully point out that, in contrast to the Examiner’s assertion, indeed the ‘373 working example (23) does not indicate a formulation within the scope of the Applicants claims.

The Applicants also wish to respectfully point out to the Examiner that a non-obvious advantage may be demonstrated by *removing* at least one previously required element from a prior art composition - if properties for the intended use of the composition are not compromised. Moreover, if properties for the intended use of a composition taught in the prior art is improved by *removing* at least one element previously believed to be integral to the utility of the composition, compelling evidence of non-obviousness exists. It is unequivocally demonstrated by this showing that **tocoferol, *per se*, as a chemical entity, reduces the aqueous solubility of podophyllotoxins, e.g., Etoposide**. This concept is contrary to what is implied by the disclosure of Lambert, *et al*, ‘373. The Applicants respectfully refer the Examiner to Table 3 of the Rule 132 Declaration (page 5) previously submitted by Dr. Valery Alakhov on June 2, 2003. Particularly, the Applicants refer the Examiner to Formulation K (pages 5-6) which corresponds to the fundamental elements of the Example 23 composition, i.e., Etoposide + tocoferol + TPGS, exemplified in Lambert, *et al*, ‘373. The Applicants next refer the Examiner to Formulation N (page 7) which corresponds to the fundamental elements of compositions of the present invention, i.e., Etoposide + TPGS. Referring back to Table 3, it is clear that the aqueous solubility of Etoposide is more than double in Formulation N when compared to Formulation K.

Accordingly, compositions of the present invention, now particularly limited to tocoferol covalently linked to a water-soluble polymer, cannot be obvious as a matter of law in view of the disclosure of Lambert, *et al*, ‘373 because an element expressly required by Lambert, namely tocoferol, *per se*, is removed to necessarily result in improved etoposide and teniposide pharmacological properties, in fact, due to increased aqueous solubility of these compounds. Lambert, *et al*, ‘373 must teach or suggest all the claim limitations. Lambert, *et al*, ‘373 encourages, teaches, and indeed requires tocoferol, the independent chemical entity, *per se*, as a necessary element in all compositions contemplated within the ‘373 disclosure. The teaching or suggestion, however, to make the Applicants’ claimed composition *and* the reasonable expectation of success must both be found in the prior art, and not based on the Applicants’

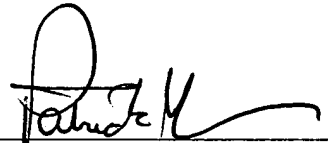
disclosure. Accordingly, the Applicants respectfully request the Examiner to withdraw the rejection.

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For all the foregoing reasons, the Applicants submit that Claims 1, 4, and 7-24 are in condition for allowance. Early action toward this end is courteously solicited. The Examiner is kindly encouraged to telephone the undersigned in order to expedite any detail of the prosecution.

The Commissioner is authorized to charge any deficiency or credit any overpayment in connection herewith to Deposit Account No.13-2165.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Patrick H. Higgins', written over a horizontal line.

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Date: October 27, 2003

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